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Therapeutic Class Review
Skeletal Muscle Relaxants

Overview/Summary

Skeletal muscle relaxants are classified by their pharmacologic properties as having either anti-spasticity or musculoskeletal (antispasmodic) activity. The anti-spasticity agents (baclofen, dantrolene and tizanidine) are used to reduce spasms that interfere with function or daily living activities, such as in cerebral palsy, multiple sclerosis and spinal cord injuries.[1] The antispasmodic agents are primarily indicated as adjuncts to rest, physical therapy and other measures for the relief of discomfort associated with acute, painful musculoskeletal disorders.[2] Musculoskeletal conditions include lower back pain, neck pain, tension headaches, fibromyalgia and myofascial pain.

The mechanism of action of these agents is not well understood. Anti-spasticity drugs, such as baclofen and tizanidine act centrally on the spinal cord or brain stem and inhibit neuronal transmission.[2,3] Baclofen is an analog of gamma aminobutyric acid (GABA) and is thought to act by stimulating this inhibitory neurotransmitter. Tizanidine is classified as an alpha-2-adrenergic agonist and it is believed to act by increasing pre-synaptic inhibition of spinal motor neurons. Dantrolene acts directly on the skeletal muscle by inhibiting the release of calcium from the sarcoplasmic reticulum, thereby inhibiting muscle contraction. Skeletal muscle relaxants with antispasmodic properties are used to relieve musculoskeletal pain. Agents that fall into this category include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone and methocarbamol. These agents are central nervous system (CNS) depressants and exert their effects either at the spinal cord or cerebral level. Controlled clinical studies have not conclusively demonstrated whether relief of musculoskeletal pain by carisoprodol, chlorzoxazone, metaxalone or methocarbamol results from skeletal muscle relaxant effects, sedative effects or a placebo effect from the drug.[3] Orphenadrine may be slightly different than the other musculoskeletal agents as it is believed to decrease skeletal muscle spasm through atropine-like effects directly on the cerebral motor neurons. Orphenadrine may also have analgesic properties that may add to its therapeutic effects.[2,3]

The use of skeletal muscle relaxants and the role of muscle spasm in the pathophysiology of lower back pain are controversial; however, 35% of patients seeking treatment for lower back pain through a primary care physician are prescribed a skeletal muscle relaxant.[1] Skeletal muscle relaxants generally appear to be more effective than placebo in providing symptomatic relief of acute lower back pain, and various skeletal muscle relaxants generally appear to be comparably effective. Skeletal muscle relaxants are generally reserved for patients who require adjunctive pharmacologic therapy and do not respond to over-the-counter analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDS). Current evidence suggests that skeletal muscle relaxants are not as tolerated (i.e. adverse CNS effects) as NSAIDS. Additionally, clinical superiority relative to NSAIDS has not been established. Most patients seeking relief of acute low back pain demonstrate improvement within 2 weeks, with substantial improvement being evident within 4 weeks. Skeletal muscle relaxants are not indicated for the treatment of chronic pain and there is no data supporting their long-term use for managing back pain.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Baclofen (previously Lioresal®)	Anti-spasticity Agents	✔

Generic Name (Trade name)	Medication Class	Generic Availability
Carisoprodol (Soma®)	Musculoskeletal Agents	✔
Chlorzoxazone (Parafon Forte®)	Musculoskeletal Agents	✔
Cyclobenzaprine (Amrix®, Flexeril®, Fexmid®)	Musculoskeletal Agents	✔
Dantrolene (Dantrium®)	Anti-spasticity Agents	✔
Metaxalone (Skelaxin®)	Musculoskeletal Agents	-
Methocarbamol (Robaxin®)	Musculoskeletal Agents	✔
Orphenadrine citrate (previously Norflex®)	Musculoskeletal Agents	✔
Tizanidine (Zanaflex®)	Anti-spasticity Agents	✔
Combination Products		
Carisoprodol/aspirin (Soma Compound®)	Musculoskeletal Agents	✔
Carisoprodol/aspirin/codeine (Soma Compound with Codeine®)	Musculoskeletal Agents	✔
Orphenadrine/aspirin/caffeine (previously Norgesic® etc.)	Musculoskeletal Agents	✔

Indications

Table 2. Food and Drug Administration Approved Indications[2,4]

Generic Name	Spastic conditions (includes spinal cord injury, traumatic brain injury, multiple sclerosis and cerebral palsy)	Musculoskeletal conditions (includes include lower back pain, neck pain, tension headaches, fibromyalgia, and myofascial pain)*	Other
Single Entity Products			
Baclofen	✔		
Carisoprodol		✔	
Chlorzoxazone		✔	
Cyclobenzaprine		✔	
Dantrolene	✔		Malignant hyperthermia
Metaxalone		✔	
Methocarbamol		✔	Spasms-tetanus
Orphenadrine citrate		✔	
Tizanidine	✔		
Combination Products			
Carisoprodol/aspirin		✔	
Carisoprodol/aspirin/codeine		✔	
Orphenadrine/aspirin/caffeine		✔	

*Adjunct to rest, physical therapy and other measures.

Pharmacokinetics

Table 3. Pharmacokinetics[4]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products*					
Baclofen	100	Hepatic; deamination	Urine and feces (85 as unchanged drug)	No	2.5-4

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Carisoprodol	Not reported	Hepatic	Urine as metabolites	Yes	8
Chlorzoxazone	100	Hepatic; glucuronidation	Urine (75) as metabolites	No	1
Cyclobenzaprine	33-55	Hepatic; oxidation and conjugation	Urine (mainly as inactive metabolites)	No	18-50†
Dantrolene	70	Hepatic; hydroxylation, N-reduction, and acetylation to less active metabolites	Urine (20) as unchanged drug and active metabolites	5-hydroxy derivative	9
Metaxalone	100	Hepatic	Urine (as metabolites)	No	2-3
Methocarbamol	100	Hepatic; dealkylation and hydroxylation	Urine (10-15 as unchanged drug and 50 as metabolites)	Glucuronide and sulfate conjugates	0.9-2
Orphenadrine citrate	95	Hepatic; almost completely metabolized to 8 metabolites	Urine, mostly as metabolites	No	14
Tizanidine	40	Hepatic; 95% metabolized to inactive metabolites	Urine (60) and feces (20)	No	2

*The kinetics for the three combination products are the same as single entity product that they contain and are listed above.
†32 hours for 15 or 30 mg extended release product and 50 hours for extended release product in patients >65 years of age.

Clinical Trials

Studies comparing the various skeletal muscle relaxants (anti-spasticity or musculoskeletal) have demonstrated that no one single agent is definitively superior over the other the agents in the class. Cyclobenzaprine is one of the more commonly used agents and new strengths have recently been developed.

Borenstein et al[5] looked at various dosages of cyclobenzaprine and compared their efficacy and side effects to placebo. Cyclobenzaprine 2.5 mg three times a day was not found to be significantly more effective than placebo. Cyclobenzaprine 5 and 10 mg were associated with significantly higher mean efficacy scores compared to placebo with equal efficacy to each other. Cyclobenzaprine 10 mg was associated with a much higher rate of sedation, potentially contributing to the development of a 7.5 mg strength tablet (Fexmid®). While all of the other strengths of cyclobenzaprine are dosed three times a day, Amrix® is an extended-release formulation available in 15 and 30 mg that is dosed once daily. This may potentially increase compliance, however the clinical significance of this is not known. Additionally, clinical trials surrounding the approval of Amrix® demonstrated a high rate of somnolence with 30 mg daily.[5]

There have been a vast number of clinical trials conducted evaluating the efficacy and safety of the skeletal muscle relaxants. However the majority of literature supporting the use of these agents was either published decades ago or are lacking in statistical significance and detail. The following studies have been identified to best portray the safety and efficacy of these medications.

Table 4. Clinical Trials

Study And Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dapas et al[6] Baclofen 10-20 mg TID-QID vs placebo	DB, PC, RCT Patients with acute LBP, muscle spasm and functional disability, <2 weeks of at least moderate severity	N=200 10 days	Primary: Improvement in pain from baseline, muscle spasms and patients assessment of improvement Secondary: Not reported	Primary: A 5-point scale was used to assess pain at baseline, day 4 and day 10. There were 63 patients in the baclofen group and 60 patients in the placebo arm that had severe pain at baseline. The mean score for local pain was 4.1, 2.6 and 2.0 in the baclofen group vs the placebo group at 4.1, 3.0 and 2.5 for baseline, day 4 and 10 respectively. Days 4 and 10 were statistically significant. The mean score for muscle spasms was 3.8, 2.2 and 1.5 in the baclofen group vs 3.8, 2.8 and 2.0 in the placebo group for days baseline, 4 and 10 respectively. Only day 10 was statistically significant. Patient outcomes were measured with the same scale and the baclofen groups mean scores (4.0, 2.7 and 1.8) vs placebo (4.0, 3.0 and 2.2) at baseline, day 4 and day 10 respectively. There was statistical significance on days 4 and 10. Secondary: Not reported
Casale et al[7] Dantrolene sodium 25 mg QID vs placebo	DB, PC, RCT Patients with acute episode of chronic LBP	N=10 4 days	Primary: Pain during maximal voluntary movements and improvement in muscle spasms Secondary: Pain behavior	Primary: Pain during maximal voluntary movements was measured by % variation on VAS on day 4. Dantrolene had 50% variation vs placebo at 8.6%. This was found to be statistically significant. Muscle spasms were measured on a 5-point scale. The proportion improved was measured on days 3 and 4. The dantrolene group improved (85%, 85%) vs placebo (10%, 30%) on days 3 and 4 respectively. Secondary: Pain behavior was reported as significantly better in the dantrolene sodium group than placebo group on day 4.
Rollings et al[8] Carisoprodol 350 mg QID	DB, RCT Patients with acute LBP of at least	N=78 7 days	Primary: Improvement in pain, muscle spasm and	Primary: VAS was used to measure pain, muscle spasms and activity impairment at baseline and at day 8. The carisoprodol group had a score of 70 for baseline and 30 for day 8 compared to 74 and 28 in the cyclobenzaprine

Study And Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cyclobenzaprine 10 mg QID	moderate intensity with muscle spasms of 7 days or less		activity impairment and overall improvement for acute LBP Secondary: Not reported	group. For muscle spasms, carisoprodol was 64 and 22 vs cyclobenzaprine at 67 and 25 for baseline and day 8 respectively. The activity impairment was similar as well with scores of 74 and 32 vs 76 and 28 for carisoprodol vs cyclobenzaprine respectively. Overall % improvement on day 8 was not statistically significant, with both groups reporting 70% improvement. There were no clinically significant differences in pain, muscle spasms, activity impairment or overall improvement in the carisoprodol vs cyclobenzaprine treated patients. Secondary: Not reported
Borenstein et al[5] STUDY 1 Cyclobenzaprine 5 mg TID vs cyclobenzaprine 10 mg TID vs placebo STUDY 2 Cyclobenzaprine 2.5 mg TID	DB, PC, PG, RCT Adult patients with acute painful muscle spasms of the lumbar or cervical region	N=1,455 Study 1: N=737 Study 2: N=668 7days	Primary: Patient-related clinical global impression of change, medication helpfulness and relief from baseline backache Secondary: Not reported	Primary: Study 1 The impression of change was rated 0-4, 0, being a worsening and 4 being marked improvement. The mean score from visit 2 and 3 were reported for both cyclobenzaprine 5 and 10 mg. Cyclobenzaprine 5 mg scored 2.29 and 2.88 and cyclobenzaprine 10 mg scored 2.30 and 2.82. Both groups were statistically significant compared to placebo at 1.91 and 2.47 at visit 2 and 3; $P \leq 0.001$. The same scale was used to evaluate patient-related medication helpfulness. Cyclobenzaprine 5 mg reported 1.62 and 2.09 and cyclobenzaprine 10 mg reported 1.62 and 2.13 which were all statistically significant ($P \leq 0.001$) compared to placebo 1.24 and 1.65 on visits 2 and 3 respectively. Relief from starting backache was rated on a score of 0-3, with 0 being no relief and 3 being a lot of relief. The mean score was reported on day 3 and day 7. Cyclobenzaprine 5 mg reported 1.74 and 2.37 and cyclobenzaprine 10 mg reported 1.83 and 2.38, which were statistically significant ($P \leq 0.03$)

Study And Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cyclobenzaprine 5 mg TID vs placebo				compared to placebo at 1.41 and 2.00 at day 3 and 7 respectively. Primary: Study 2 The impression of change was rated 0-4, 0, being a worsening and 4 being marked improvement. The mean score from visit 2 and 3 were reported for both cyclobenzaprine 2.5 and 5 mg. Cyclobenzaprine 2.5 mg scored 2.05 and 2.63 on visits 2 and 3 respectively. The 5 mg which reported 2.19 and 2.82 was statistically significant compared to placebo at 1.97 and 2.41 at visit 2 and 3; $P \leq 0.03$. The same scale was used to evaluate patient-related medication helpfulness. Cyclobenzaprine 2.5 mg reported 1.25 and 1.72 and cyclobenzaprine 5 mg reported 1.49 and 2.00. Visit 3 with cyclobenzaprine 5 mg was statistically significant ($P \leq 0.03$) compared to placebo (1.20 and 1.50) on visits 2 and 3 respectively. Relief from starting backache was rated on a score of 0-3, with 0 being no relief and 3 being a lot of relief. The mean score was reported on day 3 and day 7. Cyclobenzaprine 2.5 mg reported 1.63 and 2.03 (day 3 $P \leq 0.03$) and cyclobenzaprine 5 mg reported 1.62 and 2.24 (day 7; $P \leq 0.03$) compared to placebo at 1.29 and 1.72 at day 3 and 7 respectively. Cyclobenzaprine 2.5 mg TID was not significantly more effective than placebo. Cyclobenzaprine 5 mg and 10 mg TID were associated with significantly higher mean efficacy scores vs placebo. Cyclobenzaprine 5 mg TID was as effective as 10 mg TID, and was associated with a lower incidence of sedation. Secondary: Not reported
Stern et al[9] Methocarbamol 500 mg QID	DB, RCT, XO Patients with chronic leg pain of various etiologies	N=50 7days/ treatment arm	Primary: Patient response ratings to drug efficacy	Primary: The number of patients rating their response as excellent was 13, n=6 in the chlorphenesin group and n=7 in the carisoprodol arm. This is in contrast to the number of patients rating their response as good,

Study And Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs chlorphenesin carbamate 400 mg QID vs carisoprodol 350 mg QID vs placebo There was a washout of 1 week per treatment arm.			Secondary: Not reported	which were 60. The breakdown per group was n=17 for the chlorphenesin, n=23 for carisoprodol, n=19 for methocarbamol and n=1 for the placebo group. The only statistically significant finding reported was between carisoprodol and methocarbamol, where carisoprodol was found to be more efficacious. Secondary: Not reported
Gold et al[10] Orphenadrine 100 mg BID vs phenobarbital 32 mg BID vs placebo	DB, PC, RCT Patients with acute LBP and muscle spasms	N=20 7days	Primary: Improved pain on day 2 and overall improvement on day 2 Secondary: Not reported	Primary: Improved pain was noted in 9/20 patients in the orphenadrine, 3/20 in phenobarbital and 4/20 in placebo patients. The overall improvement was noted in 7/20, 3/20 and 0/20 patients in the orphenadrine, phenobarbital and placebo groups, respectively. There was statistical significance demonstrated in reducing pain and overall improvement with orphenadrine vs phenobarbital or placebo. Secondary: Not reported
Bragstad et al[11] Tizanidine 2 mg TID vs	DB, RCT Patients with acute LBP and muscle spasms of disc origin	N=27 7 days	Primary: Improvement in 4-point scale from baseline (pain, muscle, tension and	Primary: The average pain scores were 2.29 and 0.83 vs 2.31 and 0.73 for tizanidine and chlorzoxazone at baseline and day 7 respectively. For muscle tension the mean scores were 2.57 and 0.71 vs 2.69 and 0.44 for tizanidine vs chlorzoxazone at baseline and day 7 respectively.

Study And Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
chlorzoxazone 500 mg TID			limitation of movement) and overall perceived effectiveness by patient Secondary: Not reported	Evaluation of movement limitation was similar in both groups at 2.00 and 1.00 vs 2.15 and 0.90 for tizanidine vs chlorzoxazone. The overall effectiveness was rated as either excellent/good or moderate/poor. The results showed n=11 and n=9 in the excellent/good rating for tizanidine and chlorzoxazone, respectively. In the moderate/poor rating n=3 for both tizanidine and chlorzoxazone. There were no significant differences noted in pain, muscle tension, limitation of movement or overall effectiveness. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QID=four times daily, TID=three times daily
Study abbreviations: DB=double-blind, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: LBP=lower back pain, VAS=visual analogue scale (describes pain intensity 0-100)

Special Populations

Table 5. Special Populations [2,4]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Baclofen	Elderly may need to be started on lower doses. Not recommended for use in children under age 12.	Dose adjustment required.	No dosage adjustment required.	C	Minimal (~0.1% of oral dose).
Carisoprodol	Not approved for use in children under age 16.	No dosage adjustment required.	Start at lower doses and titrate as tolerated.	C	Unknown
Chlorzoxazone	Dosing in children based on body surface area.	No dosage adjustment required.	Start at lower doses and titrate as tolerated.	C	Unknown
Cyclobenzaprine	Extended release not recommended in elderly. Immediate release not approved in children under age 15.	No dosage adjustment required.	Mild, start with 5 mg and titrate up. Moderate-severe, not recommended.	B	Unknown
Dantrolene	Spasticity not approved for use in children under age 5.	No dosage adjustment required.	Contraindicated in active cirrhosis or acute hepatitis.	C	Unknown
Metaxalone	Not approved for use in children under age 12.	Dose adjustment required.	Dose adjustment required.	C	Unknown
Methocarbamol	Not approved for use in children under age 12.	Parenteral, contra-indicated. Oral, no dosage adjustment required.	No dosage adjustment required.	C	Infant risk is minimal.
Orphenadrine citrate	Not studied in the pediatric population.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Tizanidine	Use caution in elderly, no specific dose adjustment. Not studied in the pediatric population.	Clearance is reduced significantly- use caution, no specific dose adjustment.	Extreme caution in patients with hepatic failure.	C	Unknown

*The impact on special populations of the three combination products are the same as the single entity product that they contain and are listed above.

Adverse Drug Events

Common adverse reactions reported with the single entity skeletal muscle relaxants are summarized in Table 6. The most common adverse events are headache, drowsiness and dry mouth. The table below is not a complete list and is indicative only of those with the highest reported frequency or those listed as most common. Combination product adverse event profiles are similar to the single products that they contain and are listed below.

Table 6. Adverse Drug Events [2,4](%)

Generic Name	Adverse Event	Frequency (%)
Single Entity Products*		
Baclofen	• Confusion, headache, insomnia • Hypotension • Nausea, constipation • Transient drowsiness • Urinary frequency	1-11, 4-8, 2-7 0-9 4-12, 2-6 10-63 2-6
Carisoprodol	• Drowsiness, dizziness • Headache • Somnolence	7-8 3-5 13-17
Chlorzoxazone	• Dizziness • Lightheadedness • Malaise • Somnolence	Frequencies not reported
Cyclobenzaprine	• Drowsiness • Dry mouth • Fatigue • Headache	29-38 21-32 6 5
Dantrolene	• Constipation, diarrhea • Dizziness, headache, somnolence • Fatigue/Malaise • Lightheadedness • Visual disturbances	Frequencies not reported
Metaxalone	• Drowsiness, dizziness, headache • Nausea, vomiting, gastrointestinal upset	Frequencies not reported
Methocarbamol	• Blurred vision, conjunctivitis • Dizziness, headache, somnolence • Feeling nervous • Flushing, rash, pruritis, rash, urticaria • Indigestion, nausea, vomiting • Mild muscular incoordination	Frequencies not reported

Generic Name	Adverse Event	Frequency (%)
Orphenadrine citrate	• Blurred vision • Nausea, vomiting, xerostomia • Transient dizziness and lightheadedness • Transient syncope	Frequencies not reported
Tizanidine	• Asthenia • Dizziness • Dry mouth • Somnolence	3 2 3 3

*The adverse events of the three combination products are similar to the single products that they contain and are listed above.

Contraindications/Warnings

Carisoprodol Abuse[12]

There were about 9.88 million prescriptions for carisoprodol prescribed in 2006 (IMS Health™). Skeletal muscle relaxant action of carisoprodol may be related to its sedative properties. Recent animal studies conducted under the directive of the National Institute on Drug Abuse (NIDA) indicate that subjective effects of carisoprodol may be similar to other central nervous system depressants such as meprobamate, pentobarbital and chlordiazepoxide and it possesses rewarding effects. This data suggest that carisoprodol has abuse liability.

The onset of action of carisoprodol is rapid and effects last 4 to 6 hours. It is metabolized in the liver and excreted through the kidney. The major metabolic pathway of carisoprodol involves its conversion to meprobamate, a drug with substantial barbiturate-like biological actions. In addition to routinely documented adverse events carisoprodol may also adversely affect cardiovascular (tachycardia, postural hypotension and facial flushing), gastrointestinal (nausea, vomiting, hiccup and epigastric distress) and hematologic systems. It may cause idiosyncratic symptoms including extreme weakness, transient quadriplegia, ataxia, difficulty in speech, temporary loss of vision, double vision, dilated pupils, agitation, euphoria, confusion and disorientation. Carisoprodol overdose has resulted in stupor, coma, shock, respiratory depression and death.

Carisoprodol abuse has escalated in the last decade in the United States (US). According to 2004 National Survey on Drug Use and Health (NSUDH) data, the nonmedical use by US population aged 12 and older of Soma® (1.1%) was similar to or greater than other commonly abused schedule IV controlled drugs such as Klonopin® (1.1%), and Librium® (0.4%). With prolonged abuse at high dosage, carisoprodol can lead to tolerance, dependence and withdrawal symptoms in humans.

According to the Diversion Drug Trends, published by the Drug Enforcement Administration (DEA) on the trends in the diversion of controlled and non-controlled pharmaceuticals, carisoprodol continues to be one of the most commonly diverted drugs. Diversion and abuse of carisoprodol is prevalent throughout the country. Street prices for Soma® ranged from $1 to $5 per tablet. Diversion methods include doctor shopping for the purpose of obtaining multiple prescriptions and forging prescriptions.

According to the System to Retrieve Information from Drug Evidence (STRIDE), a federal database for the seized drug samples analyzed by DEA forensic laboratories, there were 60, 57, 58 and 54 carisoprodol cases involving seizure of 101, 117, 99 and 79 drug records in 2003, 2004, 2005 and 2006, respectively. According to the National Forensic Laboratory Information System (NFLIS), since 2000, carisoprodol has been consistently listed in the top 25 most frequent drugs identified by the state and local forensic laboratories. In 2006, a total of 3,354 analyzed items were recorded in NFLIS. Louisiana (651 items) and Texas (998 items) accounted for about a half of these items. Toxic Exposure Surveillance System (TESS) reported an increase of 25% in carisoprodol exposures from 6,656 in 2000 to 8,337 in 2005. Reports by Florida Medical Examiners indicate that carisoprodol/meprobamate related deaths in Florida increased by 51% from 208 in 2003 to 314 in 2005 and surpassed opioids such as heroin, fentanyl, hydromorphone and tramadol.

Carisoprodol is not controlled under the federal Controlled Substances Act of 1970. It is currently scheduled under state law in Alabama, Arizona, Arkansas, Connecticut, Florida, Georgia, Hawaii, Kentucky, Massachusetts, Minnesota, Nevada, New Mexico, Oklahoma, Oregon, Virginia and West Virginia.

A retrospective study was conducted in 40 patients who had used carisoprodol for at least 3 months of which 20 had history of substance abuse or dependence.[13] Among 20 patients with a history of substance abuse, 40% used carisoprodol in larger amount than prescribed, 30% used carisoprodol "for an effect other than that for which it was prescribed" and 20% attempted to obtain extra carisoprodol by prescription.

During this same study, a survey was sent to 100 physicians whose practice included prescribing of muscle relaxants. Ninety-five percent of physicians responded they were aware that meprobamate was a controlled substance associated with a potential for abuse, 39% reported that carisoprodol has abuse potential; but only 18% were aware that carisoprodol was metabolized to meprobamate.

Cyclobenzaprine: Contraindications include concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation and hypertensive crisis. Seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs. Patients who are in acute recovery phase of myocardial infarction, patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure as well as patients with hyperthyroidism should not take cyclobenzaprine.

Metaxalone: Contraindications include patients with significantly impaired renal and or hepatic function.

Orphenadrine: Contraindications include patients with glaucoma, pyloric or duodenal obstruction, steno sing peptic ulcers, prostatic hypertrophy or obstruction of the bladder neck, cardio-spasm (megaesophagus) and myasthenia gravis.

Tizanidine: Contraindications include concomitant use with fluvoxamine, ciprofloxacin or potent inhibitors of CYP1A2. Significant alterations of pharmacokinetic parameters of tizanidine including increased AUC, $t^{1/2}$, Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant administration with either fluvoxamine or ciprofloxacin. This pharmacokinetic interaction can result in potentially serious adverse events.

Dantrolene: Use has been associated with hepatotoxicity which has led to the black box listed below.

Black Box Warning for Dantrolene

WARNING
Dantrium (dantrolene sodium) has a potential for hepatotoxicity, and should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and non-fatal) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to Dantrium for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age, and in patients taking other medication(s) in addition to Dantrium (dantrolene sodium). Dantrium should be used only in conjunction with appropriate monitoring of hepatic function including frequent determination of SGOT or SGPT. If no observable benefit is derived from the administration of Dantrium after a total of 45 days, therapy should be discontinued. The lowest possible effective dose for the individual patient should be prescribed

Drug Interactions

Table 7. Drug Interactions[4]

Generic Name	Interacting Medication or Disease	Potential Result
Baclofen	Amitriptyline, imipramine and clomipramine	May induce short term memory loss.
Cyclobenzaprine	Anti-hypertensive agents	May block hypotensive effects.
Cyclobenzaprine	Estrogens	May cause hepatotoxicity.
Cyclobenzaprine	Monoamine oxidase inhibitors (MAOIs)	Contraindicated in patients currently on an MAOI due to risk of hypertensive crisis, seizures, or even death. MAOIs should not be used within 14 days following discontinuation of these drugs.
Cyclobenzaprine	Tramadol	The risk of seizures may be enhanced.
Orphenadrine	Phenothiazines	Orphenadrine may antagonize the behavioral and antipsychotic effects of phenothiazines, and enhance anticholinergic side effects.
Tizanidine	Acetaminophen	Tizanidine may delay peak plasma levels of acetaminophen.
Tizanidine	Anti-hypertensive agents	Additive effect (specifically do not use with other alpha-2 agonists, like clonidine).
Tizanidine	Oral contraceptives	Oral contraceptives may decrease the plasma clearance of tizanidine.
Carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, tizanidine	Central nervous system (CNS) depressants	May potentiate CNS and/or respiratory depression.

Dosage and Administration

Cyclobenzaprine extended release is the only agent approved for once daily dosing and is not recommended in the elderly. Many of these medications are not approved for use in children; chlorzoxazone however is dosed by body surface area, not age. Tizanidine should be used with caution in the elderly and in patients with renal and hepatic dysfunction, however no specific dose adjustment is recommended. The usual dosing regimens for the musculoskeletal agents are summarized in Table 8.

Table 8. Dosing and Administration[4]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Baclofen	Initial, 5 mg three times a day; dose may be increased by 5 mg/dose every 3 days up to 80 mg/day	Safety and efficacy in children <12 years of age has not been established.	Tablet: 10 mg 20 mg Orally disintegrating tablet: 20mg
Carisoprodol	350 mg three times a day and every night at bedtime	Safety and efficacy in children <16 years of age has not been established.	Tablet: 250 mg 350 mg
Chlorzoxazone	250-750 mg three-four times a day	20 mg/kg/day in 3-4 divided doses	Tablet: 250 mg 500 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Cyclobenzaprine	Extended release tablets: 15-30 mg daily Tablets: 5-10 mg three times a day	Safety and efficacy in children <15 years of age has not been established.	Extended release tablet: 15 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg
Dantrolene	Spasticity: 100 mg three times a day (titrated by 25 mg/week); if no response by 45 days-discontinue Malignant hyperthermia post crisis: 4-8 mg/kg/day in four divided doses for 1-3 days then titrate	Spasticity: ≥5 years, use adult weight based dosing Malignant hyperthermia: Use adult weight based dosing	Capsule: 25 mg 50 mg 100 mg
Metaxalone	Spasticity: 800 mg three-four times a day	Safety and efficacy in children <12 years of age has not been established.	Tablet: 800 mg
Methocarbamol	Acute: Titrate up as needed to 1,500 mg four times a day	Safety and efficacy in children <12 years of age has not been established.	Tablet: 500 mg 750 mg
Orphenadrine citrate	100 mg twice daily	Safety and efficacy not established in the pediatric population.	Extended release tablet: 100 mg
Tizanidine	Initial, 4 mg dose every 6-8 hours; increase dose by 2-4 mg as needed every 6-8 hours; maximum 3 doses in 24 hours	Safety and efficacy not established in the pediatric population.	Capsule: 2 mg 4 mg 6 mg Tablet: 2 mg 4 mg
Combination Products			
Carisoprodol/ aspirin	1-2 tablets four times a day	Safety and efficacy in children <16 years of age has not been established.	Tablet: 200 mg/325 mg
Carisoprodol/ aspirin/codeine	1-2 tablets four times a day	Safety and efficacy in children <16 years of age has not been established.	Tablet: 200 mg/325 mg/16 mg
Orphenadrine/ aspirin/caffeine	Initial, ½-1 tablet three-four times a day; may increase to 1-2 tablets three to four times a day	Safety and efficacy in children <16 years of age has not been established.	Tablet: 25 mg/385 mg/30 mg 50 mg/770 mg/60 mg

Clinical Guidelines

Table 9. Clinical Guidelines

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td>American College of Physicians (ACP): Guidelines for the Diagnosis and Treatment of Low Back Pain (2007)[14]</td><td>

Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work), and duration of symptoms.
The potential interventions for lower back pain are outlined below:

Interventions for the Management of Low Back Pain
<table>
<tr><th>Intervention type</th><th>Acute pain (duration < 4 weeks)</th><th>Subacute or chronic pain (duration > 4 weeks)</th></tr>
<tr><td>Self-care</td><td></td><td></td></tr>
<tr><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr>
<tr><td>Books, handouts</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Pharmacologic therapy</td><td></td><td></td></tr>
<tr><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Tricyclic antidepressants</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Nonpharmacologic therapy</td><td></td><td></td></tr>
<tr><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
<tr><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first-line options.
Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and

</td></tr>
</table>

Clinical Guideline	Recommendations
	low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen. • Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Reassess after a limited course of opioids. Evidence is insufficient to recommend one opioid over another. • Within the skeletal muscle relaxant class, the anti-spasticity medication tizanidine has been well-studied for low-back pain. However, there is little evidence for the effectiveness of baclofen and dantrolene, which are also approved for the treatment of spasticity. Other skeletal muscle relaxants are an option for short-term pain relief, but medications in this class are associated with adverse effects to the central nervous system, and risk-benefit profiles may vary substantially.
American Pain Society: **Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and American Pain Society (2007)**[15]	• Clinicians should consider the use of medications with proven benefits in conjunction with back information and self-care. Clinicians should assess the severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy. For most patients, first-line medical options are acetaminophen or NSAIDs. • Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation). There is no compelling evidence that agents in this class differ in efficacy or safety. Risk/benefit profiles vary substantially. These agents should be used with caution. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution. • Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
National Collaborating Centre for Chronic Conditions. **Multiple sclerosis: National clinical guideline for diagnosis and management in primary and secondary care (2004)**[16]	• Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. • Tizanidine should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable, other medications that may provide relief include diazepam, clonazepam and dantrolene; however their use in multiple sclerosis is not substantiated with as much clinical experience. • Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice.

Conclusions

Skeletal muscle relaxants are the most commonly prescribed medications for spasticity and musculoskeletal conditions, mainly lower back and or neck pain. The exact mechanisms of action is still vague for the various agents, but are thought to act on gamma-aminobutyric acid (GABA), at the spinal cord or cerebral level. Most of the clinical trials available are older, and do not include comparison of data to other treatment arms (ie, nonsteroidal anti-inflammatory medication).

There are some concerning side-effect profiles associated with the skeletal muscle relaxants, specifically with carisoprodol, where abuse has become an issue. The sedating adverse effect associated with cyclobenzaprine is also worrisome; however newer dosage forms may decrease the amount of sedation associated with the agent.

According to the available information, no specific agent from this class has been documented to produce a greater therapeutic effect than another agent. There are no long term studies on the safety and efficacy of these agents for musculoskeletal conditions (except anti-spasticity agents), which is mainly due to the recommendation that they be used acutely and not chronically.

Recommendations

In recognition of comparable efficacy among available skeletal muscle relaxants for the management of acute pain from musculoskeletal disorders and for spasticity, no changes are recommended to the current approval criteria.

Skelaxin® requires prior authorization with the following approval criteria:

- The patient has had a documented side effect, allergy or treatment failure with two different preferred musculoskeletal agents.

Amrix® and Fexmid® require prior authorization with the following approval criteria:

- The prescriber must provide a clinically valid reason why generic cyclobenzaprine cannot be used.

Flexeril®, Parafon Forte DSC®, and Robaxin® require prior authorization with the following approval criteria:

- The patient has had a documented side effect, allergy or treatment failure with two different preferred musculoskeletal agents (One trial must be the AB rated generic).

Carisoprodol, carisoprodol/ASA, carisoprodol/ASA/codeine, Soma®, Soma® Compound, and Soma® Compound w/codeine require prior authorization with the following approval criteria:

- The patient has had a documented side effect, allergy or treatment failure with two different preferred musculoskeletal agents. Additionally, if a brand name product is requested where an AB rated generic exists, the patient must also have had a documented intolerance to the generic product.

Dantrium® and Zanaflex® tablets require prior authorization with the following approval criteria:

- The patient must have a documented intolerance to the AB rated generic product.

Zanaflex® capsules require prior authorization with the following approval criteria:

- The prescriber must provide a clinically valid reason why generic tizanidine tablets cannot be used.

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